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Is Psilocybin an Effective Treatment to Reduce Depression and Anxiety in Cancer Patients with a Diagnosis of an Anxiety Disorder, Mood Disorder, And/Or Stress Disorder?

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Is psilocybin an effective treatment to reduce depression and anxiety in cancer patients with a diagnosis of an anxiety disorder, mood disorder, and/or stress disorder?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not psilocybin is an effective treatment to reduce depression and anxiety in cancer patients with a diagnosis of an anxiety disorder, mood disorder, and/or stress disorder.

Study design: Systematic review of three cross-over randomized placebo-controlled trials published in peer reviewed journals between 2010-2016.

Data sources: All articles were published in English and were selected from Cochrane Collaboration and PubMed based on if they were relevant to my clinical question and included patient-oriented outcomes (POEMs).

Outcomes measured: Outcomes measured included self-reported anxiety and depression via the State-Trait Anxiety Inventory (STAI) and the Beck Depression Inventory (BDI), respectively.

Results: Grob et al. (*Arch Gen Psychiatry*. 2011;68(1):71-78. doi: 10.1001/archgenpsychiatry.2010.116) found that controlled use of psilocybin when compared with placebo improved self-reported anxiety ($p<0.001$) and depression ($p=0.05$) in cancer patients. Further study by Griffiths et al. (*J Psychopharmacol*. 2016;30(12):1181-1197. doi: 0269881116675513) demonstrated that a therapeutic dose of psilocybin can statistically significantly reduce both cancer-related anxiety ($p<0.01$) and depression ($p<0.05$). Lastly, Ross et al. (*J Psychopharmacol*. 2016;30(12):1165-1180. doi: 0269881116675512 [pii]) found that single moderate dose psilocybin in conjunction with psychotherapy produced statistically significant clinical benefits in terms of reduction of anxiety ($p<0.001$) and depression ($p<0.01$) in patients with cancer and was significantly more effective than placebo with psychotherapy.

Conclusion: All three randomized controlled trials found a statistically significant reduction in self-reported anxiety via STAI scores when patients were treated with psilocybin versus placebo. Two of the three studies reported a statistically significant decrease in self-reported depression via BDI scores, with the third reporting substantial decrease but narrowly missing statistically significance. Future studies should be done that are not cross-over design in order to improve blinding and therefore validity of the study, and with larger, more diverse patient populations to increase the generalizability of these results.

Key words: Psilocybin, Depression, Anxiety

INTRODUCTION

Anxiety disorders cause feelings of excessive and persistent worry. Depression is a mood disorder characterized by feelings of depressed mood or anhedonia. Although these disorders affect many people in the general population, they are especially problematic for cancer patients. Cancer patients are prone to developing chronic, clinically significant anxiety, depressed mood, and/or decreased quality of life, with up to 40% of patients meeting the criteria for a mood disorder.[1] Anxiety and depression in cancer patients is associated with treatment non-adherence, prolonged hospitalization, higher suicide rates, decreased quality of life, increased healthcare utilization, and lower survival rates.[1,2]

Anxiety and depression in cancer patients poses significant cost and resource utilization to the healthcare system. In 2014, depressed cancer patients had 113% higher total healthcare costs than non-depressed cancer patients for the year.[3] The average healthcare charges for depressed patients was $235,337, while non-depressed patients averaged $110,650 annually.[3] This includes higher expenses for depressed patients in ambulatory care, emergency department costs, and hospital charges.[3] There are no numbers reported for cost incurred due to anxiety specifically in cancer patients. However, research in 2005 showed that a diagnosis of generalized anxiety disorder increases healthcare costs by $2,138 per patient when controlling for other factors such as demographics and other comorbidities.[4] In addition, in 2011 the mean annual number of healthcare visits for a depressed cancer patient was 29.3, which was significantly different than that of a non-depressed cancer patient at 14.7.[5]

Although the exact mechanism is not fully understood, cancer patients often face psychological, social, spiritual and existential crises as they cope with facing their own mortality, which can lead to anxiety and depression disorders.[6] The symptoms of anxiety and depression

are affected by neurotransmitters in the brain such as serotonin, epinephrine, norepinephrine, dopamine, and GABA. Symptoms of depression include anhedonia, fatigue, change in appetite, irritability, pessimism, hopelessness, helplessness, sleep disturbances, feelings of shame/guilt, and suicidal ideations. Symptoms of anxiety include apprehension, excess worry, irritability, difficulty concentration, sleep disturbances, restlessness, and easy fatiguability.

The usual treatments for anxiety and depression include both psychotherapy and pharmacotherapy. Psychotherapy may include cognitive behavioral therapy (CBT) or insight-oriented therapy. First line pharmacotherapy for anxiety and depression is selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, sertraline, citalopram, and escitalopram. Other pharmacotherapy options include serotonin–norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine. In addition, benzodiazepines may be prescribed for short-term or breakthrough anxiety symptoms such as lorazepam, alprazolam, and diazepam.

Pharmacotherapy and psychosocial interventions used for anxiety and depression in cancer patients have mixed and limited efficacy, and there is no current FDA-approved pharmacotherapy for cancer-related psychological distress.[2] Treatment effects of anti-depressants have a delayed onset, and these drugs are associated with high relapse rates and significant side effects that reduce treatment adherence in cancer patients.[2] Recent research has explored the possibility of using psilocybin, a naturally-occurring psychedelic compound found in certain mushrooms, to treat such patients. In the United States, psilocybin is an illegal drug with no current medical or pharmaceutical indications. The studies in this review explore whether psilocybin can effectively reduce self-reported anxiety and depression in patients with cancer as measured by the State-Trait Anxiety Inventory (STAI) and Beck Depression Inventory (BDI) respectively. Psilocybin has the potential to offer a novel, naturally occurring and more effective

treatment modality for these cancer patients who face significant anxiety and depression and have limited treatment options available to them. The mounting evidence showing the efficacy of psilocybin as a treatment for anxiety and depression in cancer patients is vital in order to shift public opinion about this drug and to improve the possibility of psilocybin one day being a legal pharmaceutical option for these patients in the United States. Improvement in treating anxiety and depression in cancer patients could decrease psychological distress, increase treatment adherence, decrease healthcare costs, and improve quality of life for these patients.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not psilocybin is an effective treatment to reduce depression and anxiety in cancer patients with a diagnosis of an anxiety disorder, mood disorder, and/or stress disorder.

METHODS

Three cross-over randomized placebo-controlled studies were selected in order to answer the EBM question. The population in these studies was cancer patients with a diagnosis of anxiety disorder, mood disorder, and/or stress disorder. The intervention was an active dose of psilocybin, and the comparisons included niacin 250 mg or low placebo-like dose of psilocybin.

All articles were published in English in peer-reviewed journals between the years of 2010-2016. Keywords used during the search for these articles included “psilocybin”, “depression”, and “anxiety”. Articles were selected from the databases Cochrane Collaboration and PubMed based on if they were relevant to the clinical question and included patient-oriented outcomes (POEMs). Inclusion criteria included patients with cancer and randomized placebo-control trials. Exclusion criteria included studies published prior to 2010. Statistics used in the studies consisted of Cohen’s d, t-score, and p-value. The studies chosen measured patient

outcomes of self-reported anxiety and depression. Table 1 displays the demographics and characteristics of the selected studies.

Table 1. Demographics & Characteristics of included studies

Study	Type	# Pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/ D	Inter-ventions
Griffiths[1] (2016)	Cross-over RCT	51	Mean: 56.3	Potentially life-threatening cancer & DSM-IV diagnosis of chronic adjustment disorder with anxiety, chronic adjustment disorder with mixed anxiety/ depressed mood, dysthymic disorder, GAD, and/or MDD	-Cancer with known CNS involvement -Hepatic/renal dysfunction -Severe CV illness -Pregnancy -Epilepsy -History/1st degree relative with schizophrenia, bipolar or psychotic disorder -History of alcohol/ drug dependence	5	Active psilo-cybin dose (22 or 30 mg/ 70kg)
Ross[2] (2016)	Cross-over RCT	31	Mean: 56.28 Range: 22-75	Potentially life-threatening cancer with >1-year life expectancy & DSM-IV diagnosis of Acute Stress Disorder, GAD, Anxiety disorder due to cancer, or Adjustment disorder with anxiety/depression	-<8 on HADS scale -Epilepsy, renal disease, DM, severe CV disease, liver dysfunction -History of bipolar, schizophrenia, delusional, paranoid, schizoaffective, or substance use disorders	6	Single psilo-cybin dosing session (0.3 mg/kg) with psycho-therapy
Grob[6] (2011)	Cross-over RCT	12	Range: 36-58	Advanced-stage cancer & *DSM-IV* diagnosis of acute stress disorder, GAD, anxiety disorder due to cancer, or adjustment disorder with anxiety	-Cancer with CNS involvement -Severe CV illness -Hepatic/renal dysfunction or DM -Life-time history of schizophrenia, bipolar disease, or psychotic illness -Anxiety/affective disorder within 1 year	4	Active psilo-cybin (0.2 mg/kg)

					-Chemotherapy, antiseizure, hypo-glycemic, or psycho-tropic meds in last 2 weeks		

OUTCOMES MEASURED

This EBM review compares outcomes of the intervention group to the control group through self-reported anxiety and depression. The outcomes were measured in all three studies by self-reported anxiety via the State-Trait Anxiety Inventory (STAI) and self-reported depression via the Beck Depression Inventory (BDI). The STAI is a psychological tool to measure both state and trait anxiety with 20 of the questions concentrating on trait anxiety and 20 on state anxiety. The STAI trait anxiety score is the primary measurement of anxiety treatment effects in this review. The BDI is a common psychological assessment that contains 21 questions used for patients to self-rate the severity of their depressive symptoms.

RESULTS

All three studies used similar inclusion and exclusion criteria with no notable differences. The subjects all had to be adults with a potentially life-threatening cancer diagnosis as well as a DSM-IV diagnosis related to anxiety and/or depression.[1,2,6] They could not have CNS or severe end-organ involvement/dysfunction or have any history of psychiatric illness.[1,2,6] More detailed inclusion and exclusion criteria can be seen in table 1 for each study, however there are no significant differences between the criteria.

The pilot study by Grob et al. in 2011 was a randomized placebo-controlled trial comparing moderate dose (0.2 mg/kg) psilocybin to niacin 250 mg to treat depression and anxiety in 12 cancer patients.[6] In this study, the participants acted as their own control as it was a cross-over design with each subject receiving both treatment and placebo in a randomized order.[6]

Subjects were asked to self-report their anxiety and depression via the STAI and BDI one day prior to treatment as well as at a 1 month follow up after treatment.[6] These values were compared using a 2-way analysis of variance (ANOVA) and treatment effects were expressed with t-score.[6] At 1 month follow up after psilocybin treatment, STAI scores exhibited a statistically significant decrease ($p<0.001$) as can be seen in Table 2.[6] BDI scores, although not statistically significant ($p=0.05$), still showed a substantial decrease in self-reported depression at 1 month post-treatment.[6]

In the study by Grob et al., the experimental sessions were performed in the controlled environment of a hospital clinical research unit.[6] During the sessions, subjects were left alone in a room with occasional check-ins by treatment staff.[6] After the 6-hour session was complete, the subjects discussed their experience with the staff and completed the STAI and BDI questionnaires.[6] Subjects were then continually assessed up to 6 months after the study began.[6] Eleven of the twelve study participants completed at least the first 4 months of assessments.[6]

Table 2. STAI and BDI scores in Grob et al[6]

	1 day before treatment (approximate mean)	**1 month after treatment (approximate mean)**	**T-score**	***P-value***
STAI Trait Score	43	36	4.36	$p<0.001$
BDI Score	15.5	9.5	-2.17	$p=0.05$

Building on the work of this pilot study, Griffith et al. and Ross et al. published larger studies in 2016 using psilocybin to treat depression and anxiety in cancer patients. Griffiths et al. was a randomized cross-over controlled trial comparing low placebo-like dose of psilocybin (1 or 3 mg/70 kg) to a high dose of psilocybin (22 or 30 mg/70 kg) in 51 subjects.[1] The low dose was decreased from 3 to 1 mg/70 kg after 12 subjects because of data from a dose-effect study published by Griffiths et al. in 2011. This study showed significant psilocybin effects at a dose of

5 mg/70 kg so there was concern that 3 mg/70 kg would be an active rather than a placebo dose.[1] The active high dose was lowered from 30 to 22 mg/kg after 3 subjects because of this dose-effect study data and also because 2 out of 3 of the first participants discontinued the study, one due to vomiting after pill administration and one due to "personal reasons".[1] At the conclusion of the trial, the compliance rate at the end of 6-months of follow-ups was about 90%.[1]

Griffiths et al. had participants undergo treatment in a living-room-like environment in the presence of two monitors who were blinded to treatment.[1] Subjects were encouraged to lay down wearing eye masks, and the same music was played for all participants.[1] Griffiths et al. found statistically significant decreases in both STAI scores ($p<0.01$) and BDI scores ($p<0.05$) from baseline to 5 weeks post-treatment in their pre-crossover data set as seen in table 3.[1] The group of subjects who received low placebo-like dose first were used as a control and between-group treatment effects were measured using Cohen's d.[1] Cohen's d revealed moderate difference between groups for STAI scores and large difference between groups for BDI scores.[1]

Table 3. Pre-crossover STAI and BDI scores in Griffiths et al[1]

	Baseline (mean)	**5 weeks post-session for treatment group (mean)**	**Cohen's d**	***P-value***
STAI Trait Score	47.73	34.64	0.60	$p<0.01$
BDI Score	17.77	7.00	0.81	$p<0.05$

Lastly, Ross et al. (2016) published a randomized placebo-controlled crossover trial that compares single dose psilocybin (0.3 mg/kg) to niacin (250 mg), both in combination with psychotherapy to treat anxiety and depression in patients with cancer.[2] During the experimental sessions, 29 subjects were given either active psilocybin or placebo (niacin) in conjunction with a psychotherapy session.[2] The dosing sequence was randomized and sessions occurred 7 weeks apart, with Cohen's d being used to estimate between-group treatment effects.[2] The resulting statistically significant reduction in both BDI scores ($p<0.01$) and STAI scores ($p<0.001$) at 6

weeks post-treatment for the first treatment group can be seen in table 4.[2] Cohen's d also showed statistically significant large differences between treatment and control groups in both STAI and BDI scores.[2] Compliance rate at the conclusion of the study was about 79%, however this was mostly due to disease progression in the subjects.[2]

Table 4. Decrease in pre-crossover STAI and BDI scores in Ross et al[2]

	Baseline (approximate mean)	**6-week follow up for treatment group (approximate mean)**	**Cohen's d**	***P-value***
STAI Trait Score	48	33	1.31	$p<0.001$
BDI Score	15	6.5	1.07	$p<0.01$

All three of these studies reported similar safety outcomes for psilocybin use and found that overall it was very tolerable with minimal adverse events. The most common and most significant adverse reaction in these three trials was cardiovascular effects through transient increase in blood pressure (BP) and heart rate (HR) during the sessions.[1,2,6] This adverse reaction was expected based on prior research done regarding psilocybin use. Peaking at 2 hours post-administration, Grob et al. reported statistically significant increases in systolic and diastolic BP as well as HR (table 5), while Griffiths et al. reported statistically significant increases in systolic BP and HR (table 5).[1,6] Ross et al. reported statistically significant elevation in mean systolic and diastolic BP that peaked at 142/83 mmHg at 180 minutes post-dosing of psilocybin and a statistically significant increase in mean HR that peaked at 71 bpm at 300 minutes post-dosing.[2]

Table 5. Mean BP and HR at 2 hours post-administration for treatment and control groups

	Systolic BP (mmHg)		**Diastolic BP (mmHg)**		**Heart Rate (bpm)**	
	Treatment group	**Control group**	**Treatment group**	**Control group**	**Treatment group**	**Control group**
Grob et al[6]	145	127	81	72	76	69
Griffiths et al[1]	140	115	77	68	82	68

DISCUSSION

Psilocybin is a tryptamine serotoninergic psychedelic that acts as a 5-HT_{2A} receptor agonist in active doses and produces alterations in thoughts, emotions and state of consciousness.[1,2,6] Psilocybin and its potential medicinal benefits have received very little research possibly due to the fact that it is currently illegal to use or possess in the United States. However, many cultures and religions throughout history have used psilocybin mushrooms for both their hallucinogenic and medicinal effects. More recently, psilocybin is being studied for several potential therapeutic uses in addition to anxiety and depression in cancer patients. For example, one randomized controlled trial in 2006 found that psilocybin could be used safely to produce a significant acute decrease in core obsessive compulsive disorders (OCD) symptoms in 9 subjects.[7] Although psilocybin is not currently indicated for any medicinal use in the United States, the people of Denver, Colorado voted in May 2019 to decriminalize psilocybin, signifying a possible shift in the mindset of Americans about psilocybin. With limited existing options and no FDA-approved treatment specifically for cancer-related anxiety and depression, psilocybin offers a new potential treatment modality for the psychological distress that these patients experience.

The pilot study published by Grob et al. in 2011 shed light on some of these medicinal benefits, finding a statistically significant decrease in self-reported anxiety via STAI scores ($p<0.001$) and substantial decline in self-reported depression via BDI although not statistically significant ($p=0.05$) at 1 month post-treatment.[6] This study had limited generalizability due to a small sample size of 12 participants, 11 of whom were female, but results were promising and set the stage for future research about the possible therapeutic benefits of psilocybin for cancer patients.[6]

Griffiths et al. and Ross et al. published larger and more thorough studies in 2016 using psilocybin to treat anxiety and depression in cancer patients. Griffiths et al. used low placebo-like dose psilocybin as a control, while Ross et al. used niacin 250 mg as a control with both treatment and control groups receiving psychotherapy during sessions.[1,2] Both studies found statistically significant decreases in STAI and BDI scores as well as significant differences between treatment and control groups.[1,2] However, these two studies used a very high proportion of white subjects, both over 90%.[1,2] In addition, all three of the studies in the EBM review were cross-over designs which limited blinding. Compliance rates in the studies ranged from 79-92%, with the majority of withdrawals from each of the studies being due to disease progression.[1,2,6] However, the withdrawals were not managed with worst case analysis.

CONCLUSION

When used in a controlled environment, psilocybin is effective in reducing depression and anxiety in cancer patients with a diagnosis of an anxiety disorder, mood disorder, and/or stress disorder. All three studies demonstrated statistically significant decreases in self-reported STAI scores for anxiety. Two of three studies showed statistically significant decreases in BDI scores for depression with the third having substantial decrease in BDI scores but narrowly missing statistical significance ($p=0.05$). Future research should be aimed at having larger sample sizes with a more diverse patient population to increase generalizability of the results. With larger sample sizes, there would be no need for a crossover design allowing the studies to be double-blinded, which would increase the validity of the results. The three studies in this EBM review have shown promising results for the therapeutic use of psilocybin for anxiety and depression in cancer patients. More comprehensive randomized controlled trials could increase

the evidence supporting the safe and therapeutic use of psilocybin, providing cancer patients with a new and more effective treatment for their anxiety and depression.

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